

Supplemental Amendment of the Specification for application 10/037, 718
Applicants MCGINNIS ET AL. July 15, 2006 (fax submission to 571-273-8300) 2
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The applicants hereby request an amendment to the specification of the application. The applicants believe that this amendment is in accordance with US practice including 37 CFR 1.121.

In the Specification

Please delete paragraph [0001] on page 1 and replace it with the following new paragraph:

[0001] The present patent application is a continuation-in-part of U.S. patent application Ser. No. 09/947,768 (filed Sep. 5, 2001). And 09/947,768 claims priority from U.S. Provisional No. 601230570 (filed Sep. 5, 2000). patent application Ser. No. 09/947,768 is a continuation-in-part of U.S. patent application Ser. No. 09/623,068 (filed Aug. 26, 2000). The present patent application is also a continuation-in part of patent application Ser. No. 09/623,068 (filed Aug. 26, 2000). Application 09/623,068 claims priority from PCT/US99/04376 filed (Feb. 26 1999). PCT/US99/04376 claims priority from U.S. Provisional applications No.: 60/076182 filed Feb. 27, 1998, 60/086947 filed May 27 1998, 60/076102 filed Feb. 26, 1998 and 60107673 filed Nov. 7, 1998. Each of the following patent applications are incorporated herein by reference in their individual entireties: U.S. Provisional Patent Application No. 60/230570, PCT/US99/04376, U.S. patent application Ser. No. 09/623,068, and U.S. patent application Ser. No. 09/947,768.

Please replace paragraph [0147] on page 12 with the following amended paragraph:

[0147] Sample allele frequency data for a marker and a sample is obtained by pooling DNA specimens from individuals of the sample into one or more DNA pools. An allele frequency for each of the marker's alleles is obtained for each DNA pool. In the case of a bi-allelic marker, determining the sample allele frequency for one allele essentially determines the sample allele frequency for the other allele. (For example, in some association based linkage studies, each DNA pool contains DNA from individuals of the sample with the same or similar phenotype status.) (It is also possible to obtain sample allele frequency data for a marker and a sample by calculation using genotype data at the marker for each individual in the sample.)

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Please replace paragraph [0148] on page 12 with the following amended paragraph:

[0148] Genotype data/sample allele frequency data for a marker and a sample is (1) genotype data at the marker for each individual of the sample, or (2) a combination of genotype data at the marker for one or more individuals in the sample and sample allele frequency data for the marker for the sample, or (3) sample allele frequency data for the marker for the sample. In the case of genotype data, DNA specimens from individuals are tested individually to determine genotype. In the case of sample allele frequency data DNA specimens from individuals are pooled, or sample allele frequency data is calculated using genotype data for each individual in the sample.

Please replace paragraph [0249] on page 18 with the following amended paragraph:

[0249] Companies like Affymetrix are using high density arrays of oligonucleotides attached to silicon chips or glass slides to genotype DNA from one individual at thousands of bi-allelic markers.⁸ In some of these versions of oligonucleotide technology, the strength of hybridization of oligonucleotides that differ at only one base to DNA containing an SNP are compared to determine genotype.⁹ ~~Another version of oligonucleotide technology uses oligonucleotides as PCR (Polymerase Chain Reaction) primers to obtain genotype data.¹⁰~~ Other examples of oligonucleotide technology and its uses to obtain genetic information are included in the articles cited in the end notes.¹¹ Versions of oligonucleotide technology obtain sample allele frequency data from pooled DNA or genotype data using oligonucleotides as PCR primers to obtain amplified reaction products that are detected by mass spectrometry. Another example of oligonucleotide technology is padlock probes.¹²

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Please add the following two new paragraphs after paragraph [0249]:

[0249.1] Another version of oligonucleotide technology uses oligonucleotides as PCR (Polymerase Chain Reaction) primers to obtain genotype data.¹⁰ See paragraphs, [0143] and [0144] above and see text from Schuster, H. et al (1995) Nature Genetics, 13(1), p. 100. "Genotyping was performed using the ABI PRISM Genotyping System, including the Linkage Mapping Set, PCR 9600 thermocyclers, ABI DNA Sequencers, GeneScan and Genotype software from Applied Biosystems Division, Perkin-Elmer Corporation (ABD). The PCR primers contained in the Linkage Mapping set amplify dinucleotide repeat loci spaced at approximately 10 cM. The loci were selected from the human linkage map generated by Genethon (see Gyapay, et. al. ¹⁰) based on map position, heterozygosity, and performance in routine PCR analysis. The markers in the Linkage Mapping Set are organized in 28 panels, with 9 to 17 primer pairs per panel whose products can be electrophoresed and detected in a single gel lane. Forward primers are labelled with either 6-FAM, HEX, or TET fluorescent dyes which can be distinguished due to their different spectral properties. PCR products related to specific markers are automatically identified in each lane by their molecular weight and fluorescent dye (see Zeigle, J. Application of Automated DNA sizing technology for genotyping microsatellite loci. *Genomics* 14, 1026-1031 (1992))."

[0249.2] See also text from Gyapay, et. al. (1994) Nature Genetics, 7: pp. 248-249. "**Genotyping.** Individuals from eight CEPH families were genotyped using standard procedures as described in Vignal, et. al. (A non-radioactive multiplex procedure for genotyping of microsatellite markers; in *Methods in Molecular Genetics: Gene and Chromosome Analysis* (ed. Adolph, K.W.) 211-221 (Academic Press, San Diego, 1993)). PCR amplifications were performed in 50 µl reaction mixtures, containing 40 ng of genomic DNA, 50 pmol of each primer, 125 µM dNTPs, 10 mM Tris pH 9, 50 mM KCl, 1.5 mM MgCl₂, 0.1% Triton X-100, 0.01% gelatin and 1U of *Taq* polymerase (Amersham). Amplification were carried out using the 'hot start' procedure, in which *Taq* polymerase is added to the reaction mixtures after a first denaturation step (5 min at 96 °C) after which 35 cycles of denaturation (94 °C for 40 s) and annealing (55 °C for 30s) are performed. An elongation step (2 min at 72 °C) ends the process. For each DNA sample, 16 amplification products from different markers were ethanol-precipitated and loaded together into single lanes of 6% polyacrylamide-8M urea denaturing gels. After migration, the DNA was transferred from the gel to a Hybond N⁺ nylon membrane (Amersham) by a contact blotting procedure. The markers were then revealed by successive hybridizations with one of the PCR primers which was peroxidase-labelled by modification of the ECL procedure (Amersham) and exposed to autoradiographic X-ray films."